Review Article

Relationship Between Osteoporosis and Periodontitis

Dr.V. Shivakumar,* Dr.G. Sudhir, ** Dr.S. Pavithra Priyadarshini,*** Dr.M. Shanmugam,****

Chettinad Health City Medical Journal 2012; 1(1): 19 - 27

Dr.V.Shivakumar M.D.S., is working as HOD & Professor in the Department of Periodontology in Chettinad Dental College & Research Institute for past 3 years. He graduated from Government Dental College, Chennai and did his Masters in Periodontics, Annamalai University, Chidambaram. He has publication in national and international journals. He has participated and delivered guest lectures in over national and international conferences. He actively participates in community health services and research oriented programmes.

* Professor & HOD, ****Reader, Chettinad Dental College & Research Institute, Kelambakkam, Chennai.
**Registrar, Ganga Medical Centre & Hospital, Coimbatore. ***Dental Surgeon, Coimbatore.

Abstract

Periodontitis is a complex disease which may be accelerated or dampened by the innate differences among individuals and changes in environmental factors. The diagnosis is based on clinical signs and symptoms, as well as medical and dental history, the importance of determination and integration of subject-level factors, microbial composition, systemic immune response, and gingival tissue inflammatory mediator responses is being increasingly discussed. From being considered as a condition confined to the oral cavity, it is now known to branch out to the entire human body. Good oral health for good general health is gaining paramount importance. At this juncture, we aimed to bring to light the subtle connection between the two debilitating conditions osteoporosis and periodontitis through this review article. Osteoporosis is a silent disease, reflected only in a low bone density, till a fracture occurs. With increasing longevity of the Indian population, it is now being realized that, osteoporotic fractures are a major cause of morbidity and mortality in the elderly. Periodontitis and other periodontal inflammatory conditions are implicated in alveolar bone loss leading to tooth mobility and tooth loss. We attempt to answer the question of whether dental osteopenia is a local manifestation of osteoporosis having similar etiology and risk factors, or it is an independent process depending primarily on factors that cause periodontal disease.

Key-words: Osteoporosis, Periodontitis, Tooth mobility, Oral health, Risk factor.

Introduction

Osteoporosis is characterized by decreased bone mass and increased fracture susceptibility. Osteoporosis is a disease in which the density and quality of bone are reduced, leading to weakness of the skeleton and increased risk of fracture, particularly of the spine, wrist and hip. Osteoporosis and associated fractures are an important cause of mortality and morbidity[1]. The risk of fracture increases with age, especially in women above fifty years of age (Figure 1).

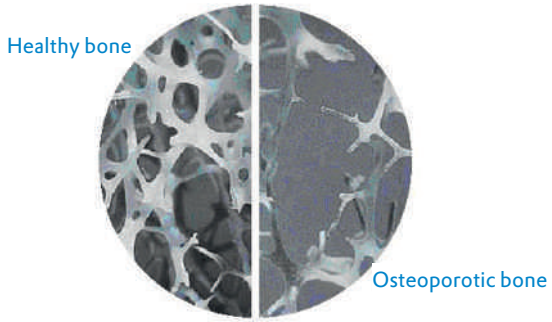

Fig.1 Healthy vs osteoporotic bone

Emotional morbidity in the form of depression, reluctance, may accompany osteoporosis. 1 out of 8 males and 1 out of 3 females in India suffers from osteoporosis, making India one of the largest affected countries in the world. In most Western countries, the peak incidence of osteoporosis occurs at about 70-80 years of age, in India it may afflict those 10-20 years younger, at age 50-60[2].

Osteoporosis can be classified as osteoclast mediated or type I and osteoblast mediated or type II. The type I is characterized by a rapid phase of bone loss predominantly involving the trabecular pattern seen in recently postmenopausal women. Women are affected 6% more frequently than men. In type II women are twice as affected as male and are related to aging, chronic calcium deficiency, increased parathyroid hormone activity and decreased bone formation[3].Osteoporosis is often called the "silent disease" because bone loss occurs without symptoms. In many cases, the first "symptom" is a broken bone. Patients with osteoporosis may not know that they have the disease until their bones become so weak that a sudden strain, bump, or fall causes a hip fracture or a vertebra to collapse. Collapsed vertebra may initially be felt or seen in the form of severe back pain, loss of height, or spinal deformities such as kyphosis, or severely stooped posture[4] (Figure 2).

The evaluation of a patient in whom osteoporosis is suspected should include a thorough medical history, imaging and laboratory studies, and possibly bone histomorphometry. A routine X-ray can reveal osteoporosis of the bone because the bones appear much thinner and lighter than normal bones.

Dual energy X ray absorptiometry (DXA) is the best current test to measure BMD. The test is quick and painless. The risk of fractures generally is lower in people with osteopenia when compared with those with osteoporosis but, if bone loss continues, the risk for fracture increases.

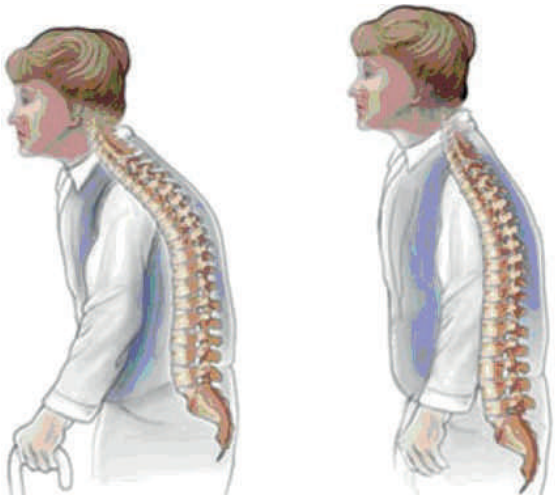

Fig.2 Age related kyphosis of spine

Risk Factors for Osteoporosis

The Non-modifiable risk factors include

- Personal history of fracture as an adult
- History of fracture in first-degree relative
- Caucasian race
- Advanced age
- Gender
- Dementia
- Poor health/frailty

The Potentially modifiable risk factors include

- Current cigarette smoking
- Low body weight (<127 lbs.)
- Estrogen deficiency
- Early menopause (<age 45) or bilateral ovariectomy
- Prolonged premenopausal amenorrhea (>1 Year)
- Low calcium intake (lifelong)
- Alcoholism
- Caffeine
- Impaired eyesight despite adequate correction
- Recurrent falls
- Inadequate physical activity

Medication

Many medications including corticosteroids, anticonvulsants, and heparin are known to decrease bone density. Prolonged corticosteroid therapy, especially in a dose of prednisone greater than 7.5 mg per day, is known to triple the risk of fracture and is the most common cause of drug-induced osteoporosis. A very recent report links accelerated bone loss to the antiretroviral class of drugs.

Drugs associated with an increased risk of generalized osteoporosis:

- Aluminum
- Anticonvulsants
- Cigarette smoking
- Cytotoxic drugs
- Excessive alcohol
- Excessive thyroxine
- Glucocorticoids and adrenocorticotropin
- Gonadotropin-releasing hormone agonists
- Heparin
- Lithium
- Tamoxifen (premenopausal use)

Bone Metabolism

Bone is a living matrix that is in a constant state of flux and under direct cellular control. Bone is formed by osteoblasts, which are cells of marrow stromal origin[5]. Bone resorption is under the control of osteoclasts. These large, multinucleated cells arise from macrophage precursors. They cause bone resorption by first isolating a segment of bone surface, thereby creating a Howships lacuna. Next, acidification solubilizes the mineral phase by means of a carbonic anhydrase mechanism, and, finally, the production of acid proteases allows for the enzymatic degradation of the organic components, including the collagen.

Frost first described the bone metabolic unit as coupled process in which resorption precedes formation[6]. Bone remodeling proceeds throughout life, and an imbalance in this process that either enhances resorption or impairs formation ultimately leads to a net loss of bone mass.

The greater the peak bone mass achieved, the better the chance of avoiding osteoporosis later in life. After peak bone mass is reached, bone loss normally occurs at the rate of 0.3 percent per year in men and 0.5 percent per year in women. A rate of bone loss of 2 to 3 per cent per year (an 8 percent decrease in trabecular bone and a 0.5 per cent decrease in cortical bone) begins at the onset of menopause. This rate continues for a period of six to ten years and then declines to a rate of 0.5 percent per year. While all adults lose bone with age, osteoporosis develops in only 20 to 30 per cent of women and 10 to 20 per cent of men who are more than sixty-five years old[7]. Many hormones directly affect bone metabolism[8]. A major one is vitamin D, a steroid hormone that plays a critical role in calcium metabolism 1,25-dihydroxyvitamin D increases absorption of calcium across the gut by maturing the villus lining cells of the intestine and stimulating them to produce

calcium-binding protein. Active vitamin D augments parathyroid hormone recruitment of osteoclasts for bone resorption by acting as a maturation hormone for the macrophage stem cell.

The second prominent hormone in bone metabolism is parathyroid hormone[8]. Parathyroid hormone responds to low ionic calcium levels by stimulating the retention of calcium and excretion of phosphate by the kidneys. In addition, parathyroid hormone indirectly increases the absorption of calcium across the gut by stimulating the conversion of 25-hydroxyvitamin D to the active metabolite 1,25- dihydroxyvitamin D in the medullary portion of the kidneys. Indirectly, by means of the osteoblast (the coupling factor leading to increased osteoclast activation), parathyroid hormone leads to bone resorption. Hence, parathyroid hormone indirectly leads to the absorption of calcium across the gut, the resorption of calcium from bone, and increased retention of calcium within the kidneys[9].

Calcitonin is a calcitropic peptide produced in the parafollicular cells of the thyroid gland. Calcitonin responds to elevated serum ionic calcium levels by decreasing the number and activity of osteoclasts[10]. Calcitonin also functions as a neuropeptide and has analgesic effects. It primarily decreases bone resorption and secondarily causes a transient increase in bone formation by means of a still unknown mechanism.

A normal balance of oestrogen and progesterone is critical for the maintenance of bone mass. Young women who have episodes of amenorrhoea or oligomenorrhoea before peak bone mass is attained lose 2 per cent of bone mass per year instead of gaining 2 to 4 per cent per year as they would normally[11]. This loss is oestrogen-dependent, and the bone mass that is lost is not regained once normal menstrual cycles are resumed. The level of circulating oestrogen declines after menopause. Some women have a rapid acceleration of bone loss secondary to increased bone-remodeling, with bone resorption exceeding bone formatio[n11]2

Association of Osteoporosis and Periodontitis

Periodontitis is charecterised by inflammation and loss of connective tissue and alveolar bone. Like osteoporosis, it is a silent disease causing symptoms until late in the disease process when mobile teeth, abscesses and tooth loss may occur. Both osteoporosis and periodontal disease share many risk factors and since both are bone resorptive diseases it has been hypothesized that osteoporosis could influence progression of periodontal disease. In the last ten years a large amount of research was done on the influence of systemic bone mass loss in osteoporosis on the periodontal disease appearance. Krall et al[13] thinks that alveolar bone loss in patients with lower bone mineral density can be faster and less resistant to therapy than in patients with normal bone density. Jeffcoat came to the conclusion that a quarter of postmenopausal women have faster bone mass loss (5-8% a year) and are at higher risk for alveolar bone loss and periodontal disease[14].

Another study showed that the average values of pocket depth in healthy patients (M = 3.51) are statistically significantly lower (at 98% significance level) than the average values of pocket depth in patients with osteoporosis (M = 4.14). The presence of the combined type of bone resorption is more frequent (at 97% significance level) in patients with osteoporosis (f = 5) in comparison to healthy ones[15]. Tezal et al., Pilgrae et al. and Chohayeb connect skeleton bone mass density BMD with alveolar bone loss and also with evident clinical connection loss and they conclude that there is a connection between postmenopausal osteoporosis and periodontal status. The average pocket depth value is statistically significantly different in relation to skeleton BMD[16, 17, 18].

The results arrived in a study by Hildebolt, Shen et al. and Von Wowen et al. were that BMD does change with age and that the change is accompanied by alveolar bone changes[19,20,21]. Geurs et al. studied the connection between systemic bone loss (measured by DXA) and periodontal disease (measured by periodontal pocket depth). They concluded that the patients with osteoporosis have greater epithelial connective tissue loss than the patients without osteoporosis, i.e. that the greatest epithelial connective tissue loss is in patients with both periodontal disease and osteoporosis. Geurs et al. considered osteoporosis or lower values of skeleton BMD should be considered as a risk factor for the development of periodontal disease[22]. In their study, Wactawski-Wende,[23] discovered a significant connection between periodontal connective tissue loss, as an indicator for periodontitis, and skeleton osteoporosis measured by DXA, especially in postmenopausal women. Klemetti et al. studied the postmenopausal women with significantly deep priodontal pockets and detected greater BMD loss in relation to the patients with shallow periodontal pocket or no periodontal pockets. On the basis of their research they concluded that there is a relation between BMD and periodontal disease[24]. A study has shown that after fifty years of age the porosity of the mandibular cortical bone increases markedly especially in the alveolar bone, at the same time there is a decrease in bone mass[25]. These changes are greater in women than in men and this is reflected in the fact that women have a lower mandibular BMD than men. This sex difference in BMD value is also observed in other bones. It has been suggested that this increase in alveolar bone porosity in combination with local factors could be of etiological importance in the rate of periodontal alveolar bone loss which leads to periodontal disease. Some authors have experimentally concluded that in postmenopausal women BMD is related to interproximal alveolar bone loss. This conclusion points at postmenopausal osteopenia as a possible risk factor for periodontal disease in postmenopausal women[26].

Another study has shown that women with high calculus apposition and low BMD had greater clinical gingival attachment loss than women with normal BMD and similar calculus apposition[27]. Still other authors have reported that serum oestradiol supplementation, in early menopausal osteoporotic women, reduces gingival inflammation and attachment loss[28].

A study performed on digitized periapical radiographs of the maxilla and mandible obtained from osteoporotic patients and normal controls lends support to the hypothesis that osteoporotic patients present an altered trabecular pattern in the jaw bones when compared to normal controls[29].

Radiographic evaluation of alveolar bone loss was conducted in a 2-year longitudinal clinical study on 21 women with normal BMD of the lumbar spine, and 17 women with osteoporosis or osteopenia of the lumbar spine at baseline. These 38 patients had a history of periodontitis and were non-smokers. The results of this study showed that osteoporotic/osteopenic women exhibited a higher frequency of alveolar bone height loss ($p<0.05$) and crestal ($p<0.025$) and subcrestal ($p<0.03$) density loss relative to women with normal BMD. Additionally it was shown that oestrogen deficiency in the osteoporotic/osteopenic women was associated with increased alveolar bone crestal density loss. This study data suggests that oestrogen deficiency and osteoporosis/osteopenia could be considered potential risk factors for alveolar bone loss in postmenopausal women with periodontitis[30].

Pilgram et al have concluded that there is no definite association between clinical attachment level and BMD of the lumbar spine and the femur. They also conclude that there may be a weak association between BMD and longitudinal changes in attachment level[31]. Histomorphometric and micro radiographic studies showed that people aged more than 50 years experience significant changes in the osseous tissue, occurring in mandibular trabecular and cortical bone tissue, and increasing porosity of the cortical layer results in the decrease in bone mass[32]. E Manzke et al[33] raised a hypothesis that systemic imbalance in bone resorption and deposition may manifest itself in the alveolar bone earlier than in other bones. During a long period of the research, a number of comparative studies on different bones (e.g. spinal vertebrae and mandible, mandible and radius, wrist, thigh-bone, and other bones of the skeleton) were performed[34], and it was suggested to pay attention to the influence of systemic factors that are responsible for the development of the osteoporotic process and to the relationship of these factors with the local ones that increase the alveolar resorption of mandible. Due to its anatomical–morphological properties, maxilla was rarely used in the studies of changes in osseous tissues.

J. J. Groen et al[35] thought that spinal vertebrae and the mandible had similar muscle fixation, and therefore, they compared radiograms and raised a hypothesis that radiograms of alveolar processes could be good indicators for the diagnosis of systemic osteoporosis . These authors have even proposed a term – "alveolar or periodontal osteoporosis". P. J. Kribbs in 1983[36] and 1989[37]and N. Von Wowern[38] in 1994 concluded that mandibular osseous mass correlated with the total skeletal bone mass. The majority of performed studies showed that a relationship existed between total skeletal bone mass and the amount of oestrogens in the organism, and that diminution of oestrogen levels affected the bone density of the jaws.

A. R. Becker[39] who performed his investigation in 1997, determined a negative correlation between the number of remaining teeth and the time of the beginning of menopause in women of postmenopausal age in whom no hormone replacement therapy was applied. R. E. Persson in 1998[40] and J. B. Payne in 1999[41] studied older women who underwent hormone replacement therapy and concluded that periodontium in such women was healthier than in those who did not receive such treatment. A.Taguchi in 1995[42] and L. Birkenfeld in 1999[43] performed a descriptive study on women who had experienced spinal fractures. The majority of them had periodontitis and few remaining teeth in the oral cavity. The authors suggested that there could be a high percentage of people with periodontal diseases among those with osteoporosis. Not all studies confirmed the presence of a relationship between periodontal diseases and osteoporosis, In a study of 70 year old women 15 subjects with osteoporosis were compared to 21 subjects with normal BMD. No statistically significant difference was found in gingival bleeding, probing pocket depths, gingival recession or marginal bone level between the women with osteoporosis and the women with normal BMD[44].

In a report by Elders et al.,[45]lumbar BMD and metacarpal cortical thickness were compared to alveolar bone height on bitewing radiographs and clinical parameters of periodontitis. No significant relation was found between bone mass measurements and alveolar bone height and periodontal parameters. The mean age of this study was[46]- 55 yrs, consisting of younger population, and could have contributed to the lack of correlation. In August 1992, a relationship between oral and skeletal osteoporosis was confirmed, and an agreement on the necessity of radiological diagnosis was made 44. In 1992, the US National Health Institute ordered special studies for the determination of the relationship between oral condition and osteoporosis. The application of the panoramic radiogram test for people with osteoporosis for the confirmation of the diagnosis of periodontitis was among the set objectives. M. G. Perno in 2002 stated that it was well known how to treat osteoporosis or periodontal diseases separately, but there was no clear definition concerning how to treat patients who have both diseases . The question of whether curative means and measures applied for osteoporosis are also effective in periodontitis still remains unanswered46.

M. Tezal et al[47]states that changes in the systemic bone density also simultaneously entail changes in the height and the density of the alveolar bone and changes in the height of the clinical junction of periodontal tissues . F. Grodstein[48] in his studies found that women who had osteoporosis and underwent oestrogen therapy had a significantly higher probability to preserve their teeth, whereas women with osteoporosis who did not undergo any oestrogen therapy and poorly performed oral hygiene procedures had a high risk of losing their teeth. This risk may be reduced by prescribing treatment with hormone preparations.

A cross-sectional study in a group of[50] normal women aged 20-90 years was done and it was inferred that the mandibular bone mass correlated with the bone mass

at spine and wrist. In another study a comparison of 85 osteoporotic women and 27 normal women were compared. The osteoporotic group had less mandibular bone mass and density and a thinner cortex at the gonion than the normal group. In another study done by the same author on 85 osteoporotic post-menopausal women the total body calcium, bone mass at radius and bone density at the spine correlated with mandibular mass.

Prevention and Treatment

The goal of treatment of osteoporosis is the prevention of bone fractures by reducing bone loss or, preferably, by increasing bone density and strength. Although early detection and timely treatment of osteoporosis can substantially decrease the risk of future fractures, none of the available treatments for osteoporosis are complete cures. The following are osteoporosis treatment and prevention measures. Calcium is one of the most widely used agents in the treatment of osteoporosis[49]. Calcium supplementation in the older population may be most effective when the baseline calcium intake is less than 400 milligrams per day, for those who have an intestinal malabsorption syndrome, or in combination with an exercise regimen[50]. Calcium supplementation is helpful for patients who have type-II osteoporosis, especially when the therapy is combined with vitamin-D supplementation[51]. A marked decrease in the rate of fractures of the hip was demonstrated in a study of elderly patients from France who had received dietary supplements of calcium and vitamin-D. This decrease occurred even though little difference was noted in bone mass, a finding that raises the possibility that the calcium and vitamin-D supplementation had improved the quality of bone or had decreased the prevalence of secondary hyperparathyroidism[52].

Vitamin-D stimulates bone formation and intestinal calcium absorption; vitamin-D supplementation therefore may improve calcium balance. In addition, vitamin-D may positively influence bone density in healthy individuals who do not have vitamin-D deficiency or osteoporosis by suppressing parathyroid hormone activity[53]. Several recent studies have shown that the oral administration of calcitriol and some of its synthetic precursors, notably alfa calcidol (1-alpha-hydroxyvitamin D3), can correct mild secondary hyper parathyroidism, reduce bone loss, and prevent fractures of the hip[54, 55]

Oestrogen deficiency plays a prominent role in the pathogenesis of osteoporosis. Estrogen inhibits bone resorption and positively affects calcium balance, either directly, by stimulating the estrogen receptors in bone, or indirectly, by suppressing the production of bone-resorbing cytokines; inhibits osteoclast formation and function and can also extend the lifespan of osteoblasts and osteocytes[56, 57]. The administration of estrogen to postmenopausal women not only prevents bone loss but also protects against vertebral and femoral fractures, with a greater effect on the spine [58]. Discontinuation of the therapy is followed by an immediate resumption of bone loss at a rate similar to that in women who have not received such therapy[59].

Dose of estrogen required to prevent bone loss is 0.625 milligram, but half of this dose may suffice when it is combined with calcium supplementation[60]. Prolonged use of estrogen appears to increase the risk of breast cancer by 30 per cent[61, 62], an increase roughly from eleven to fourteen instances of breast cancer per 100 women. The concomitant administration of progestin eliminates the risk of uterine cancer, and continuous therapy with a combination of progestin and estrogen can minimize cyclical uterine bleeding in older women 60. Most of the cardiovascular benefits associated with estrogen are preserved when progestin is given cyclically, but the continuous use of progestin diminishes some of the cardiovascular benefits of estrogen. Selective estrogen receptor modulators provide benefits of estrogen without its unwanted side effects. The mechanism of action such as that of raloxifene is similar to that of the estrogens. Reduction of fracture was seen in first year of treatment but no effect was found on the risk of non-vertebral fractures [63]. Similar to estrogen therapy, an increase in the incidence of deep vein thrombosis was observed. New selective estrogen receptor modulators are researched and may be available in the near future.

Calcitonin typically is administered by means of subcutaneous injection and also has been shown to be effective in intranasal, rectal, and transdermal forms, although there may be erratic patterns of absorption with the nasal route. The analgesic effects of the newly released nasal form are similar to those of the other forms. Reginster et al.[64] conducted a three-year randomized placebo-controlled study in which women in whom menopause had taken place six to thirty-six months previously were given either calcium alone or the same amount of calcium in addition to calcitonin by means of nasal administration.

Bisphosphonates are stable, active analogs of pyrophosphate that both inhibit osteoclastic resorption and depress bone turnover[65]. Etidronate and newer bisphosphonates, including alendronate, pamidronate, residronate, taludrinate, and clonodrate, currently are the most extensively investigated agents in osteoporosis research[66]. Etidronate is most effective during the first two years of therapy[67]. Bisphosphonates appear to be effective in the five-year period of rapid bone turnover that occurs after menopause. Bisphosphonates primarily act on trabecular bone and are less effective in preventing the loss of compact bone as well as fractures of the hip[68].

The second-generation agents are more potent and yet cause less inhibition of mineralization than Etidronate [69]. Alendronate, recently approved by the Food and Drug Administration, appears to prevent vertebral bone loss in patients who have osteoporosis and does not alter the mechanical properties of bone4. In addition, it appears to continue to work even after it is no longer being administered. Rossini et al.[70] recently reported that lumbar bone-mineral density increased by 3.7 ± 1.7 per cent (average and standard deviation) after six months of Alendronate therapy and did not change six and twelve months after the cessation of treatment.

The occurrence of osteonecrosis of the jaw with the use of bisphosphonate is a concern to dental community. Osteonecrosis of the jaws occurs more commonly in the mandible but has also been reported in the maxilla, and appears to be highly associated with periodontitis, other oral infections, and extraction of the affected teeth in majority of the reported cases. In addition the signs and symptoms that may occur before the appearance of clinically evident osteonecrosis include changes in the health of the periodontal tissues, non- healing mucosal ulcers, loose teeth, unexplained soft tissue infection. The role of bisphosphonates in osteonecrosis of the jaw needs to be further evaluated.

In contrast to the antiresorptive drugs described previously, fluoride causes osteoblast proliferation and stimulates new bone formation. Researchers have found substantial increases in trabecular bone in patients who had received fluoride[71]. Enthusiasm for fluoride has been tempered by studies that have shown impaired bone mineralization and increased rates of fractures of the hip and vertebrae despite increased bone density in the lumbar spine[72]. Patients in whom osteoporosis is treated with fluoride often have a calcium deficiency because of increased mineralization of trabecular bone. This renders the patients vulnerable to secondary hyperparathyroidism. Vitamin-D supplementation can correct the calcium deficiency while potentiating the effect of fluoride on the osteoblast; this allows the dose of fluoride to be decreased and thereby minimizes its side effects 73. The ideal role of fluoride in the future may be to augment bone density at the initiation of therapy before switching to antiresorptive agents for the long-term maintenance of bone density. At the present time, however, the use of fluoride is considered experimental.

Conclusion

The current studies point at a possible correlation between osteoporotic bone loss and periodontal bone loss. Further studies are required in this direction to facilitate answers to many questions. Is dental osteopenia a local manifestation of osteoporosis having similar etiology and risk factors, or whether it is an independent process depending primarily on factors that cause periodontal disease? What research techniques are precise enough for determining bone density in the mandible? How does the osteoporotic process damage different skeletal structures? Is periodontitis the first prognostic sign of osteoporotic changes in spine and long bones? Periodontist and Orthopaedicians should understand the effects of osteoporosis on both systemic and oral health. These two health care providers working hand in hand could increase the awareness among people, offer early diagnosis of the disease, elucidate solutions and fabricate a treatment modality to bring these two debilitating conditions in check.

REFERENCE

1) International Osteoporosis Foundation (IOF) http://www.iofbonehealth.org/patients-public/about osteoporosis.html

2) Damodaran P, Subramaniam R, Omar SZ, Nadkarni P, Paramsothy M., Singapore Med J. 2000 Sep; 41(9): 431-5, "Profile of a menopause clinic in an urban population in Malaysia

3) American Academy of Orthopaedic Surgeons: A position statement: prevention of hip fractures. Rosemont, Illinois, The American Academy of Orthopaedic Surgeons, 1993

4) National Instititutes of Health Osteoporosis and Related Bone Disease-National Resource Center http://www.osteo.org 2004

5) Lane, J. M.; Cornell, C. N.; and Healey, J. H.: Orthopaedic consequences of osteoporosis. In Osteoporosis. Etiology, Diagnosis and Management, pp. 433-455. Edited by B. L. Riggs and L. J. Melton, III. New York, Raven Press, 1988.

6) Frost, H. M.: Bone Remodeling Dynamics. Springfield, Illinois, Charles C Thomas, 1963

7) Kassem, M.; Mosekilde, L.; and Eriksen, E. F.: 1,25-dihydroxyvitamin D3 potentiates fluoride-stimulated collagen type I production in cultures of human bone marrow stromal osteoblast-like cells. / Bone and Min. Res., 8:1453-1458,1993

8) Cummings, S. R.; Kelsey, J. L.; Nevitt, M. C; and O'Dowd, K. J.: Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol. Rev., 7:178-208,1985.

9) Lane, J. M., and Healey, J. H. [editors]: Diagnosis and Management of Pathological Fractures. New York, Raven Press, 1993.

10) Wong, G. L.: Skeletal effects of parathyroid hormone. In Bone and Mineral Research/4, edited by W. Peck. Ed. 4, pp. 103-130. Amsterdam, Elsevier, 1986.

11) Austin, L. A., and Heath, H., Ill: Calcitonin: physiology and pathophysiology. New England J. Med., 304: 269-278,1981.

12) Cann, C. E.; Cavanaugh, D. J.; Schnurfield, K.; and Martin, M. C: Menstrual history is the primary determinant of trabecular bone density in women runners [abstract]. Med. and Sci. Sports and Exerc, 20 (Supplementum): 559,1988.

13) Krall EA, The Oral Effects of Osteoporosis. Nutr Clin Care. 2001;4:22-7.

14) Jeffcoat M. The association between osteoporosis and oral bone loss. J Periodontol. 2005;76(11 Suppl):2125-32.

15) Bone levels in patients with osteoporosis and periodontal disease Mirjana Gojkov-Vukelić1, Mirjana Malić1, Sanja Hadžić1, Lidija Lincender2 Acta Medica Academica 2007; 36: 76-81

16) Tezal M, Wactawski-Wende J, Grossi SG, Ho AW, Dunford R, Genco RJ. The relationship between bone mineral density and periodontitis in postmenopausal women. J Periodontol. 2000;71(9):1492-8.

17) Pilgram TK, Hildebolt CF, Yokoyama-Crothers N, Dotson M, Cohen SC, Hauser JF et al. Relationship between longitudinal changes in radiographic alveolar bone height and probing depth measurement: Data from postmenopausal women. J Periodontol. 1999;70:829-33.

18) Chohayeb AA. Influence of osteoporosis on the oral health of menopausal women. General Dentistry. 2003;258-.

19) Hildebolt CF, Pilgram TK, Yokoyama-Crothers N, Vannier MW, Dotson M, Muckerman J, et al. Alveolar bone height and postcranial bone mineral density: Negative effects of cigarette smoking and parity. J Periodontal. 2000;71: 683-9.

20) Shen EC, Gau CH, Hsieh Yd, Chang CY, Fu E. Periodontal status in post menopausal osteoporosis : a preliminary clinical study in Taiwanese women. J Chin Med Assoc. 2004;67:389-93.

21) Von Wowern N. General and oral aspects of osteoporosis: a review. Clin Oral Invest. 2001;5:71-82.

22) Geurs NC, Lewis CE, Jeffcoat MK. Osteoporosis and periodontal disease progression. Periodontology.2000;32:105-10.

23) Wactawski-Wende J. Periodontal diseases and osteoporosis: association and mechanisms. Ann Periodontol. 2001;6:197-208.

24) Klemetti E, Collin HL, Forss H, Markkanen H&Lassila V. Mineral status of skeleton and advanced periodontal disease. J Clin Periodontol. 1994;21:184-8.

25) Hildebolt,CF.Osteoporosis and oral bone loss.Dento-Maxillo-fac Radiol 1997;26:3-15.

26) Tezal, M et al. The relationship between bone mineral density and periodontitis in postmenopausal women. J Periodontol 2000;71:1492-8.

27) Ronderos, M et al. Associations of periodontal disease with femoral bone mineral density and estrogen replacement therapy: cross-sectional evaluation of US adults from NHANES III. J Clin Periodontol 2000;27:778-86.

28) Reinhardt, RA et al. Influence of estrogen and osteopenia/osteoporosis on clinical periodontitis in postmenopausal women. J Periodontol 1999;70:823-8.

29) White, SC; Rudolph, DJ. Alterations of the trabecular pattern of the jaws in patients with osteoporosis. Oral Sur Oral Med Oral Pathol Oral Radiol Endod 1999;88:628-35.

30) Payne, JB; Reinhardt, RA; Nummikoski, PV; Patil, KD.Longitudinal alveolar bone loss in postmenopausal osteoporotic/osteopenic women. Osteoporosis International 1999;10:34-40.

31) Pilgram TK et al. Relationships between clinical attachment level and spine and hip bone mineral density: data from healthy postmenopausal women. J Periodontol 2002;73:298-301.

32) Hildebolt CF. Osteoporosis and oral bone loss. Dentomaxillofac Radiol 1997;26:3-15.

33) Manzke E, Chesnut CH III, Wergedal JE, Baylink DJ, Nelp WB. Relationship between local and total bone mass in osteoporosis. Metabolism 1975;24:605-15.

34) Haimov-Kochman R, Kochman T, Stabholz A, Hochner- Celinkier D. Bisphosphonate and estrogen replacement therapy for postmenopausal periodontitis. IMAJ 2004;6:173-6.

35) Groen JJ, Duyvensz F, Halsted JA. Diffuse alveolar atrophy of the jaw (non-inflammatory form of paradental disease) and presenile osteoporosis. Geront Clin 1960;2:68-86.

36) Kribbs PJ, Smith DE, Chesnut CH 3rd. Oral findings in osteoporosis. Part I. Measurement of mandibular bone density. J Prosthetic Dentistry 1983;50(4):576-9

37) Kribbs PJ, Chesnut C, Ott SM, et al. Relationships between mandibular and skeletal bone in an osteoporotic population. J Prosthetic Dentistry 1989;62:703-6.

38) von Wowern N, Klausen B, Kollerup G. Osteoporosis: a risk factor in periodontal disease. J Periodontol 1994;65(12):1134-8.

39) Becker AR, Handick KE, Roberts WE, Garetto LP. Osteoporosis risk factors in female dental patients. A preliminary report. J Indiana Dental Assoc 1997;76:15-9.

40) Persson RE, Persson GR, Kiyak HA, Powel LV. Oral health and medical status in dentate low-income older persons. Spec Care Dentist 1998;18:70-7.

41) Payne JB, Reinhardt RA, Nummikoski PV, Patil KD. Longitudinal alveolar bone loss in postmenopausal osteoporotic/ osteopenic women. Osteoporosis Int 1999;10:34-40.

42) Taguchi A, Tanimoto K, Suei Y, Otani K, Wada T. Oral signs as indicators of possible osteoporosis in elderly women. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80:612-6.

43) Birkenfeld L, Yemini M, Kase NG, Birkenfeld A. Menopauserelated alveolar bone resorption: a review of relatively unexplored consequences of estrogen deficiency. Menopause 1999; 6:129-33.

44) Hildebolt CF. Osteoporosis and oral bone loss. Dentomaxillofac Radiol 1997;26:3-15

45) Elders PJ,Habetts LL,Netelenbos JC, Linden LW,Stelt PF The relationship between periodontitis and systemic bone loss in women between 46 and 55 years of age J Clinical Periodontol1992:19 492-6

46) Goldi MP. Osteoporosis. Periotrends 2002;7:34-7.

47) Tezal M, Wactawsky-Wende J, Grossi SG, Ho AW, Dunford R, Genco RJ. The relationship between bone mineral density and periodontitis in postmenopausal women. J Periodontol 2000;71:1492-98.

48) Grodstein F, Colditz GA, Stampfer MJ. Post-menopausal hormone use and tooth loss: a prospective study. J Am Dent Assoc 1996;127:370-7.

49) Heaney, R.P.: Calcium in the prevention and treatment of osteoporosis. J.Intern.Med., 231:169-180,1992

50) Dawson-Hughes, B.; Dallal, G. E.; Krall, E. A.; Sadowski, L.; Sahyoun, N.; and Tannenbaum, S.: A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. New England J. Med., 323: 878-883,1990.

51) Buckwalter, J. A.; Glimcher, M. J.; Cooper, R. R.; and Recker, R.: Bone biology. Part II: formation, form, modeling, remodeling, and regulation of cell function. J. Bone and Joint Surg., 77-A: 1276-1289, Aug. 1995.

52) Chapuy, M. C; Arlot, M. E.; Duboeuf, F.; Brun, J.; Crouzet, B.; Arnaud, S.; Delmas, P. D.; and Meunier, P. J.: Vitamin D3 and calcium to prevent hip fractures in the elderly women. New England J. Med., 327:1637-1642,1992

53) Khaw, K. T.; Scragg, R.; and Murphy, S.: Single-dose cholecalciferol suppresses the winter increase in parathyroid hormone concentrations in healthy older men and women: a randomized trial. Am. J. Clin. Nutr., 59:1040-1044,1994

54) Orimo, H.; Shiraki, M.; Hayashi, T.; and Nakamura, T.: Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D3. Bone and Min., 3: 47-52,1987.

55) Menczel, J.; Foldes, J.; Steinberg, R.; Leichter, I.; Shalita, B.; Bdolah-Abram, T.; Kadosh, S.; Mazor, Z.; and Ladkani, D.: Alfacalcidol (alpha D3) and calcium in osteoporosis. Clin. Or/hop., 300: 241-247,1994.

56) Hui, S. L.; Slemenda, C. W.; and Johnston, C. C, Jr.: Baseline measurement of bone mass predicts fracture in white women. Ann. Intern.Med., 111:355-361,1989.

57) Jilka, R. L.; Hangoc, G.; Girasole, G.; Passeri, G.; Williams, D. C; Abrams, J. S.; Boyce, B.; Broxmeyer, H.; and Manolagas, S. C: Increased osteoclast development after estrogen loss: mediation by interleukin-6. Science, 257: 88-91,1992.

58) Ettinger, B.; Genant, H. K.; and Cann, C. E.: Long-term estrogen replacement therapy prevents bone loss and fractures. Ann. Intern. Med., 102:319-324,1985.

59) Buckwalter, J. A.; Glimcher, M. J.; Cooper, R. R.; and Recker, R.: Bone biology. Part II: formation, form, modeling, remodeling, and regulation of cell function. J. Bone and Joint Surg., 77-A: 1276-1289, Aug. 1995.

60) Session, D. R.; Kelly, A. C; and Jewelewicz, R.: Current concepts in estrogen replacement therapy in the menopause. Fertil. and Sterii, 59:277-284,1993.

61) Colditz, G. A.; Egan, K. M.; and Stampfer, M. J.: Hormone replacement therapy and risk of breast cancer: results of epidemiologic studies. Am../. Obstet. and Gynec, 168:1473-1480,1993.

62) Colditz, G. A.; Hankinson, S. E.; Hunter, D. J.; Willet, W. C; Manson, J. E.; Stampfer, M. J.; Hennekens, C; Rosner, B.; and Speizer, F. E.: The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. New England J. Med., 332:1589-1593,1995

63) Riggs B.L., Hartmann L.C. Selective estrogen receptor modulators: Mechanism of action and application to clinical practice New England J. Med.,2003.348;618-29

64) Reginster, J. Y.; Denis, D.; Deroisy, R.; Lecart, M. P.; De Longueville, M.; Zegels, B.; Sarlet, N.; Noirfalisse, P.; and Franchimont, P.:Long-term (3 years) prevention of trabecular postmenopausal bone loss with low-dose intermittent nasal salmon calcitonin. J. Bone ana'Min. Res., 9:69-72,1994.

65) Endo, Y.; Nakamura, M.; Kikuchi, T.; Shinoda, H.; Takeda, Y.; Nitta, Y.; and Kumagai, K.: Aminoalkybisphospbonates, potent inhibitorsof bone resorption, induce a prolonged stimulation of histamine synthesis and increase macrophages, granulocytes, and osteoclasts in vivo. Calcif. Tissue Internal, 52: 248-254,1993

66) Ott, S. M.: Clinical effect of bisphosphonates in involutional osteoporosis./ Bone and Min. Res., 8 (Supplement 2): S597-S606,1993.

67) Harris, S. T.; Watts, N. B.; Jackson, R. D.; Genant, H. K.; Wasnich, R. D.; Ross, P.; Miller, P. D.; Licata, A. A.; and Chesnut, C. H., Ill:Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. Am. J. Med., 95: 557-567,1993.

68) Storm, T.; Thamsborg, G.; Steiniche, T.; Genant, H. K.; and Sorensen, O. H.: Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. New England J. Med., 32:1265-1271,1990.

69) Toolan, B. C; Shea, M.; Myers, E. R.; Hayes, W. C; Thompson, D. D.; Seedor, J. G.; Quartuccio, H.; Klein, H. J.; Jackson, R.; Fioravanti, C; Gibson, R. E.; Clair, J.; and Rodan, G. A.: The effect of long term alendronate treatment on vertebral strength in ovariectomized baboons and rats [abstract]./ Bone and Min. Res., (Supplement 1): S248,1991.

70) Rossini, M.; Gatti, D.; Zamberian, N.; Braga, V.; Dorizzi, R.; and Adami, S.: Long-term effects of a treatment course with oral alendronate of postmenopausal osteoporosis. J. Bone and Min. Res, 9:1833-1837,1994.

71) Boivin, G.; Dupuis, J.; and Meunier, P. J.: Fluoride and osteoporosis. In Osteoporosis: Nutritional Aspects. World Review of Nutrition and Dietetics, edited by A. P. Simopoulos and C. Galli. Vol. 73, pp. 80-103. Basel, Switzerland, Karger, 1993.

72) Riggs, B. L.; Hodgson, S. E; O'Fallon, W. M.; Chao, E. Y.; Wahner, H. W.; Muhs, J. M.; Cadel, S. L.; and Melton, L. J., Ill: Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. New England J. Med., 322: 802-809,1990.

73) Heaney, R. P.; Recker, R. R.; and Saville, P. D.: Menopausal changes in bone remodelling. /. Lab. and Clin. Med., 92:964-970,1978.

Chettinad Hospital & Research Institute